SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Cisplatin 1 mg/ml Concentrate for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of concentrate for solution for infusion contains 1 mg of Cisplatin.

10 ml of concentrate for solution for infusion contains 10 mg of Cisplatin
25 ml of concentrate for solution for infusion contains 25 mg of Cisplatin
50 ml of concentrate for solution for infusion contains 50 mg of Cisplatin
100 ml of concentrate for solution for infusion contains 100 mg of Cisplatin

Excipients with known effect: Each ml of solution contains 3.5 mg of sodium. For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion

Clear, colourless to pale yellow solution in an amber glass vial, which is practically free from particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Cisplatin is intended for the treatment of:

- advanced or metastasised testicular cancer
- advanced or metastasised ovarian cancer
- advanced or metastasised bladder carcinoma
- advanced or metastasised squamous cell carcinoma of the head and neck

- advanced or metastasised non-small cell lung carcinoma
- advanced or metastasised small cell lung carcinoma.
- Cisplatin is indicated in the treatment of cervical carcinoma in combination with other chemotherapeutics or with radiotherapy.
- Cisplatin can be used as monotherapy and in combination therapy

4.2 Posology and method of administration

Posology
Adults and children:

The cisplatin dosage depends on the primary disease, the expected reaction, and on whether cisplatin is used for monotherapy or as a component of combination chemotherapy. The dosage directions are applicable for both adults and children.

For monotherapy, the following two dosage regimens are recommended:

< < Single dose of 50 to 120 mg/m² body surface every 3 to 4 weeks;
< 15 to 20 mg/m²/day for five days, every 3 to 4 weeks.

If cisplatin is used in combination therapy, the dose of cisplatin must be reduced. A typical dose is 20 mg/m² or more once every 3 to 4 weeks.
For treatment of cervical cancer cisplatin is used in combination with radiotherapy. A typical dose is 40 mg/m² weekly for 6 weeks.

For warning and precautions to be considered prior to the start of the next treatment cycle (see section 4.4).

In patients with renal dysfunction or bone marrow depression, the dose should be reduced adequately (see section 4.3).

The cisplatin solution for infusion prepared according to instructions (see section 6.6.) should be administered by intravenous infusion over a period of 6 to 8 hours.

Adequate hydration must be maintained from 2 to 12 hours prior to administration until minimum 6 hours after the administration of cisplatin. Hydratation is necessary to cause sufficient diuresis during and after treatment with cisplatin. It is realised by intravenous infusion of one of the following solutions:
sodium chloride solution 0.9%

Method of administration
Cisplatin 1 mg/ml sterile concentrate is to be diluted before administration. For

instructions for dilution of the product before administration see section 6.6.

The diluted solution should be administered only intravenously by infusion (see below). For administration, any device containing aluminium that may come in contact with cisplatin (sets for intravenous infusion, needles, catheters, syringes) must be avoided.

Hydration prior to treatment with cisplatin:

Intravenous infusion of 100 to 200ml/hour for a period of 6 to 12 hours, with a total amount of at least 1litre.

Hydration after termination of the administration of cisplatin:

Intravenous infusion of another 2 litres at a rate of 100 to 200 ml per hour for a period of
6 to 12 hours.

Forced diuresis may be required should the urine secretion be less than 100 to 200 ml/hour after hydration. Forced diuresis may be realised by intravenously administering 37.5g mannitol as a 10% solution (375 ml mannitol solution 10%), or by administration of a diuretic if the kidney functions are normal.
The administration of mannitol or a diuretic is also required when the administrated cisplatin dose is higher than 60 mg/m2 of body surface.

It is necessary that the patient drinks large quantities of liquids for 24 hours after the cisplatin infusion to ensure adequate urine secretion.

4.3. Contra-indications

Hypersensitivity to cisplatin or to any of the excipients listed in section 6.1 or other platinum containing compounds.

Cisplatin induces nephrotoxicity which is cumulative. It is therefore contraindicated in patients with pre-existing renal impairment.

Cisplatin has also been shown to be cumulatively neurotoxic (in particular ototoxic) and should not be given to patients with pre-existing hearing impairment.

Cisplatin is also contraindicated in myelosuppressed patients and those who are dehydrated.

Patients receiving cisplatin should not breast feed (see section 4.6).

Concurrent administration of yellow fever vaccine is contraindicated.

4.4. Special warnings and precautions for use

This agent should only be administered under the direction of oncologists in specialist units under conditions permitting adequate monitoring and surveillance. Supportive equipment should be available to control anaphylactic reactions.

Cisplatin reacts with metallic aluminium to form a black precipitate of platinum. All aluminium
containing IV sets, needles, catheters and syringes should be avoided.

The solution for infusion should not be mixed with other drugs or additives.

Appropriate monitoring and management of the treatment and its complications are only possible if adequate diagnosis and exact treatment conditions are available.

1.
Nephrotoxici
ty

Cisplatin produces severe cumulative nephrotoxicity. Which may be potentiated by aminoglycoside antibiotics. Cisplatin should not be given more frequently than once every 3-4 weeks.

Repeat courses of cisplatin should not be given unless levels of serum creatinine are below 1.5 mg/100 ml (130 µmol/l) or blood urea below 55 mg/100 ml (9 mmol/l), and circulating blood levels are at an acceptable level. Since the renal toxicity of cisplatin is cumulative, measurement of BUN, serum creatinine or GFR should be performed prior to initiating therapy and prior to each subsequent course.

Adequate pre-treatment and ‘during treatment’ hydration should be ensured and such agents as mannitol given to minimise hazards of renal toxicity. A urine output of 100 mL/hour or greater will tend to minimize cisplatin nephrotoxicity. This can be accomplished by prehydration with 2 litres of an appropriate intravenous solution, and similar post cisplatin hydration (recommended 2,500 mL/m2/24 hours). If vigorous hydration is insufficient to maintain adequate urinary output, an osmotic diuretic may be administered (eg, mannitol).

The serum creatinine, BUN and creatinine clearance should be measured prior to initiating therapy and monitored throughout treatment with cisplatin.

2.Neuropathies

Severe cases of neuropathies have been reported.
These neuropathies may be irreversible and may manifest by paresthesia, areflexia and a proprioceptive loss and a vibration perception. A loss of motor function has also been reported. A neurologic examination must be carried out at regular intervals.
Neurotoxicity appears to be cumulative.

3. Ototoxicity

Ototoxicity has been observed in up to 31% of patients treated with a single dose of cisplatin
50mg/m2, and is manifested by tinnitus and/or hearing loss in the high frequency range (4000 to 8000Hz). Decreased ability to hear conversational tones may occur occasionally. Ototoxic effect may be more pronounced in children receiving cisplatin. Hearing loss can be unilateral or bilateral and tends to become more frequent and severe with repeated doses; however, deafness after initial dose of cisplatin has been reported rarely. Ototoxicity may be enhanced with prior simultaneous cranial irradiation and may be related to peak plasma concentration of cisplatin. It is unclear whether cisplatin induced ototoxicity is reversible. Careful monitoring by audiometry should be performed prior to initiation of therapy and prior to subsequent doses of cisplatin. Vestibular toxicity has also been reported (see section 4.8).

Since ototoxicity of cisplatin is cumulative, audiometric testing should be performed prior to initiating therapy and prior to each subsequent course of the drug (see section 4.8).

4. Allergic phenomena

As with other platinum-based products, hypersensitivity reactions appearing in most cases during perfusion may occur, and necessitate discontinuation of the perfusion and an appropriate symptomatic treatment. Cross reactions, sometimes fatal, have been reported with all the platinum compounds (See sections 4.3 and 4.8).

5. Hepatic function and haematological formula

The haematological formula and hepatic function must be monitored at regular intervals.

6. Carcinogenic potential

In humans, in rare cases the appearance of acute leukaemia has coincided with use of Cisplatin, which was in general associated with other leukaemogenic
agents.

Cisplatin carcinogenic in mice and rats (see section 5.3).

7. Injection site reactions

Injection site reactions may occur during the administration of cisplatin. Given the possibility of extravasation, it is recommended to closely monitor the infusion site for possible infiltration during drug administration. A specific treatment for extravasation reactions is unknown at this time.

WARNING

This cytostatic agent had a more marked toxicity than is usually found in antineoplastic chemotherapy.

Renal toxicity, which is above-all cumulative, is severe and requires particular precautions during administration (see sections 4.1 and 4.8).

Nausea and vomiting may be intense and require adequate antiemetic treatment. Close supervision must also be carried out with regard to ototoxicity, myelodepression and anaphylactic reactions (see section 4.8).

Preparation of the intravenous solution

Warning

As with all other potentially toxic products, precautions are essential when handling the cisplatin solution. Skin lesions are possible in the event of accidental exposure
to the product. It is advisable to wear gloves. In the event the cisplatin solution comes into contact with the skin or mucous membranes, wash the skin or mucous membranes vigorously with soap and water.

Conforming to the procedures appropriate for the manipulation and elimination of cytostatic agents is recommended.

Before administering the solution to the patient, verify the clarity of the solution and the absence of particles.

This medicinal product contains 3.5 mg sodium per ml, equivalent to 38.3% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
Cisplatin may be further prepared for administration with sodium-containing solutions (see section 6.6) and this should be considered in relation to the total sodium from all sources that will be administered to the patient.

4.5. Interactions with other medicinal products and other forms of interaction

Cisplatin can be used in combination with other cytostatics with corresponding mechanisms of action. Additive toxicity might occur in such cases.

Myelosuppression induced by cisplatin will be additive to existent impairment or to the similar toxicity of other agents such as cephaloridine, frusemide, aminoglycosides, etc., administered concurrently.

Nephrotoxic substances:
Concomitant administration of nephrotoxic (e.g. cephalosporins, aminoglycosides or
Amphotericin B or contrast media) or ototoxic (e.g. aminoglycosides) medicinal produ
cts will potentiate the toxic effect of cisplatin on the kidneys. Nephrotoxicity might be exacerbated by aminoglycoside antibiotics, administered simultaneously or 1-2 weeks after treatment with cisplatin. The use of other potentially nephrotoxic drugs (e.g. amphotericin) is not recommended during treatment with cisplatin. During or after treatment with cisplatin caution is advised with predominantly renally eliminated substances, e.g. cytostatic agents such as bleomycin and methotrexate, because of potentially reduced renal elimination.

The renal toxicity of ifosfamide may be greater when used with cisplatin or in

patients who have previously been given cisplatin.

Reduction of the blood's lithium values was noticed in a few cases after treatment with cisplatin
combined with bleomycin and etoposide. It is therefore recommended to monitor the lithium values.

Ototoxic substances:

Concomitant administration of ototoxic (e.g. aminoglycosides, loop diuretics) medicinal products will potentiate the toxic effect of cisplatin on auditory function. Except for patients receiving doses of cisplatin exceeding 60 mg/m2, whose urine secretion is less than 1000 ml per 24 hours, no forced diuresis with loop diuretics should be applied in view of possible damage to the kidney tract and ototoxicity.

Ifosfamide may increase hearing loss due to cisplatin.

Weakened live vaccines:
Yellow fever vaccine is strictly contraindicated because of the risk of fatal systemic vaccinal disease (see section 4.3.). In view of the risk of generalised illness, it is advisable to use an inactive vaccine if available.

Oral anticoagulants:
In the event of simultaneous use of oral anticoagulants, it is advisable regularly to check the
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Antihistamines, Phenothiazines and others:
Simultaneous use of antihistamines, buclizine, cyclizine, loxapine, meclozine, phenothiazines, thioxanthenes or trimethobenzamides may mask ototoxicity symptoms (such as dizziness and tinnitus).

Pyroxidine + altretamine combination:
During a randomised study of the treatment of advanced ovarian cancer, the response time was unfavourably affected when pyridoxine was used in combination with altretamine
(hexamethylmelamine) and Cisplatin.

Paclitaxel:
Treatment with cisplatin prior to an infusion with paclitaxel may reduce the clearance of paclitaxel by 33% and therefore can intensify neurotoxicity.

Anticonvulsive substances/Anti-epileptics:
Serum concentrations of anticonvulsive medicines may remain at sub therapeutic levels during treatment with cisplatin. For example; in patients receiving cisplatin

and phenytoin, the serum level of phenytoin might be reduced. This is probably due to reduced absorption and/or increased metabolism. One should monitor the levels of phenytoin in plasma, and adjust the dose accordingly.

Cisplatin may interact with aluminium (see section 4.2).

4.6 Fertility, pregnancy and lactation

Pregnancy
Cisplatin may be toxic to the foetus when administered to a pregnant woman. The safe use of cisplatin in human pregnancy has not been established. Studies in animals have shown reproductive toxicity (see section 5.3). Cisplatin should not be used during pregnancy unless the clinician considers the risk to the individual patient to be justified.

During treatment with Cisplatin and for a minimum of the following 6 months, appropriate measures must be taken to avoid pregnancy; this applies to patients of both sexes.

Genetic consultation is recommended if the patient wishes to have children after ending treatment.

Breast-feeding
Cisplatin is excreted in breast milk. Patients treated with cisplatin must not breastfeed.

Fertility
Since a treatment with cisplatin may cause irreversible infertility, it is recommended that men, who wish to become fathers in the future, ask for advice regarding cryoconservation of their sperm prior to treatment.

4.7 Effects on ability to drive and use machines

No studies on the effects on ability to drive and use machines have been performed.

Nevertheless, the profile of undesirable effects (like nephrotoxicity) may influence the ability to drive vehicles and use machinery.

4.8. Undesirable Effects

The most frequently reported adverse events (>10%) of cisplatin were haematological (leukopenia, thrombocytopenia and anaemia), gastrointestinal (anorexia, nausea, vomiting and diarrhoea), ear disorders (hearing impairment), renal disorders (renal failure, nephrotoxicity, hyperuricemia) and fever.

Serious toxic effects on the kidneys, bone marrow and ears have been reported in up to about one third of patients given a single dose of cisplatin; the effects are generally dose-related and cumulative. Ototoxicity may be more severe in children.

Frequencies are defined using the following convention:

Very common (≤1/10); common (≤1/100 to <1/10); uncommon (≤1/1,000 to <1/100); rare (≤1/10,000 to ≤1/1,000); very rare (≤1/10,000), not known (cannot be estimated from the available data).

Table of Adverse Drug Events Reported During Clinical or Postmarketing Experience (MedDRA terms).

System Organ Class	Frequency	MedDRA term
Infections and infestations	Not known	Infection[a]
	Common	Sepsis
Blood and lymphatic system disorders	Very common	Bone marrow failure, thrombocytopenia, leukopenia, anaemia
	Not known	Coombs positive haemolytic anaemia, thrombotic microangiopathy (haemolytic uremic syndrome), neutropenia
Neoplasm benign, malignant, and unspecified	Rare	Acute leukaemia
Immune system disorders	Uncommon	Anaphylactoid[b] reaction
Endocrine disorders	Not known	Blood amylase increased, inappropriate antidiuretic hormone secretion
Metabolism and nutrition disorders	Not known	Dehydration, hypokalaemia, hypophosphatemia, hyperuricemia, hypocalcaemia, tetany
	Uncommon	Hypomagnesaemia
	Very common	Hyponatraemia
Nervous system disorders	Not known	Cerebrovascular accident, haemorrhagic stroke, ischaemic stroke ageusia, cerebral arteritis, Lhermitte's sign, myelopathy, autonomic neuropathy
	Rare	Convulsion, neuropathy peripheral, leukoencephalopathy, reversible posterior leukoencephalopathy syndrome
Eye disorders	Not known	Vision blurred, colour blindness acquired, blindness cortical, optic neuritis, papilledema, retinal pigmentation
Ear and labyrinth disorders	Uncommon	Ototoxicity
	Not known	Tinnitus, deafness
Cardiac disorders	Not known Common	Cardiac disorder Arrhythmia, bradycardia, tachycardia
	Rare	Myocardial infarction
	Very rare	Cardiac arrest
Vascular disorders	Common	Venous thromboembolism
	Not known	Raynaud's phenomenon

Gastrointestinal disorders	Not known	Vomiting, nausea, anorexia, hiccups, diarrhoea
	Rare	Stomatitis
Hepatobiliary disorders	Not known	Hepatic enzymes increased, blood bilirubin increased
Respiratory, thoracic and mediastinal disorders	Not known	Pulmonary embolism
Skin and subcutaneous tissue disorders	Not known	Rash, alopecia
Musculoskeletal, connective tissue and bone disorders	Not known	Muscle spasms
Renal and urinary disorders	Not known	Renal failure acute, renal failure[c] , renal tubular disorder
Reproductive system and breast disorders	Uncommon	Abnormal spermatogenesis
General disorders and administration site condition	Not known	Pyrexia (very common), asthenia, malaise, injection site extravasationd

a: Infectious complications have led to death in some patients.

b: Symptoms include facial edema (PT-face oedema), flushing, wheezing, bronchospasm, tachycardia, and hypotension will be included in the parentheses for anaphylactoid reaction in the AE frequency table.

c: Elevations in BUN and creatinine, serum uric acid, and/or a decrease in creatinine clearance are subsumed under renal insufficiency/failure.

d: Local soft tissue toxicity including cellulitis, fibrosis, and necrosis (common) pain (common), oedema (common) and erythema (common) as the result of extravasation.

Nephrotoxicity
Renal toxicity has been shown in 28-38% of patients treated with a single dose of cisplatin 50 mg/m2. Renal toxicity becomes more prolonged and severe with repeated courses of the drug.

Gastrointestinal toxicity
Nausea and vomiting occur in the majority of patients, usually starting within 1 hour of treatment and lasting up to 24 hours. Anorexia, nausea and occasional vomiting may persist for up to a week.

Ocular Toxicity
There have been reports of optic neuritis, papilledema and cerebral blindness following treatment with cisplatin. Improvement and/or total recovery usually occurs following immediate discontinuation. Blurred vision and altered colour perception have been reported after the use of regimens with higher doses of cisplatin or greater dose frequencies than those recommended.

Ototoxicity
Ototoxicity has occurred in up to 31% of patients treated with a single dose of cisplatin 50 mg/m2. Ototoxicity may be more severe in children and more frequent and severe with repeated doses. Careful monitoring should be performed prior to

initiation of therapy and prior to subsequent doses of cisplatin.

Unilateral or bilateral tinnitus, which is usually reversible, and/or hearing loss in the high frequency range may occur.

The overall incidence of audiogram abnormalities is 24%, but large variations exist. These abnormalities usually appear within 4 days after drug administration and consist of at least a 15 decibel loss in pure tone threshold. The damage seems to be cumulative and is not reversible. The audiogram abnormalities are most common in the 4000- 8000 Hz frequencies.

Haemotoxicity

Myelosuppression is observed in about 30% of patients treated with cisplatin. Leukopenia and thrombocytopenia are more pronounced at higher doses. The nadirs in circulating platelets and leucocytes generally occur between days 18-23 (range 7.3 to 45) with most patients recovering by day 39 (range 13 to 62). Leukopenia and thrombocytopenia are more pronounced at doses greater than 50 mg/m2. Anaemia (decreases of greater than 2 g% haemoglobin) occurs at approximately the same frequency, but generally with a later onset than leukopenia and thrombocytopenia. Subsequent courses of cisplatin should not be instituted until platelets are present at levels greater than 100,000/mm3 and white cells greater than 4,000/mm3. A high incidence of severe anaemia requiring transfusion of packed red cells has been observed in patients receiving combination chemotherapy including cisplatin.

Anaphylaxis

Reactions possibly secondary to cisplatin therapy have been occasionally reported in patients who were previously exposed to cisplatin. Patients who are particularly at risk are those with a prior history or family history of atopy. Facial oedema, wheezing, tachycardia, hypotension and skin rashes of urticarial non-specific maculopapular type can occur within a few minutes of administration. Serious reactions seem to be controlled by I.V. adrenaline, corticosteroids or antihistamines.

Neurotoxicity

Neurotoxicity may occur. It is cumulative and may be irreversible. It is generally characterised by neuropathies, but seizures and taste loss have occurred.

Peripheral neuropathies with paraesthesia in both upper and lower extremities, tremor and loss of taste have been observed in some patients, generally those treated with repeated courses.

Hypomagnesaemia and Hypocalcaemia
Hypomagnesaemia occurs quite frequently with cisplatin administration, while hypocalcaemia occurs less frequently. The loss of magnesium seems to be associated with renal tubular damage which prevents resorption of this cation. Where both electrolytes are deficient, tetany may result. It does not appear to be dose related. Monitoring of electrolytes is necessary.

Electrolyte Disturbances
Hyponatraemia, hypokalaemia and hypophosphatemia can occur.

Hyperuricemia
Hyperuricemia occurring with cisplatin is more pronounced with doses greater than 50 mg/m2. Allopurinol effectively reduces uric acid levels.

Cardiac and Vascular Disorders
Cardiac reactions including tachycardia and arrhythmia have been reported. Vascular toxicities coincident with the use of cisplatin in combination with other antineoplastic agents have been reported rarely. These events may include myocardial infarction, cerebrovascular accident, thrombotic microangiopathy (Haemolytic uremic syndrome) or cerebral arteritis.

Other Toxicities
There are also reports of Raynaud's phenomenon occurring in patients treated with the combination of bleomycin, vinblastine and with or without cisplatin. It has been suggested that hypomagnesaemia developing with the use of cisplatin may be an added, although not essential factor, associated with this event. However the cause of this Raynaud's phenomenon is currently unknown.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme. Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9. Overdose

CAUTION IS ESSENTIAL IN ORDER TO PREVENT AN INADVERTANT OVERDOSE.

Overdosage can be expected to cause the toxic effects described above, but to an exaggerated degree. Adequate hydration and osmotic diuresis may help reduce the toxicity of cisplatin if administered promptly following overdosage. Convulsions may be treated with appropriate anticonvulsants.

An acute overdose of Cisplatin may result in renal failure, liver failure, deafness, ocular toxicity (including detachment of the retina), significant myelosuppression, untreatable nausea and vomiting and/or neuritis. Renal function, cardiovascular function and blood counts should be monitored daily in order to assess the potential toxicity to these systems. Serum magnesium and

calcium levels should be carefully monitored as should symptoms and signs of voluntary muscle irritability. If symptomatic tetany develops, electrolyte supplements should be administered. Serum liver enzymes and uric acid should also be monitored daily after an acute overdose. An overdose may be fatal.

There is no specific antidote in the event of an overdosage of Cisplatin. Even if haemodialysis is initiated 4 hours after the overdose it has little effect on the elimination of cisplatin from the body following a strong and rapid fixation of Cisplatin to proteins.

Treatment in the event of an overdose consists of general support measures.

If fever develops during prolonged myelosuppression, appropriate presumptive antibiotic coverage should be instilled after cultures have been obtained.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents, Platinum compounds, ATC code: L01XA01

Cisplatin has biochemical properties similar to those of bifunctional alkylating agents. The drug inhibits DNA-synthesis by producing intrastrand and interstrand cross- links in DNA. Protein and RNA synthesis are also inhibited to a lesser extent.

Although the principal mechanism of action of cisplatin appears to be inhibition of DNA synthesis, other mechanisms, including enhancement of tumour immunogenicity may be involved in its antineoplastic activity. Cisplatin also has immunosuppressive, radiosensitising, and antimicrobial properties. Cisplatin does not appear to be cell-cycle specific.
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5.2 Pharmacokinetic properties

Absorption
There is good uptake of cisplatin by the kidneys, liver and intestine. More than 90% of platinum containing species remaining in the blood are bound (possibly irreversibly) to plasma proteins.

Penetration into the CSF is poor although significant amounts of cisplatin can be detected in intracerebral tumours. Distribution
The clearance of total platinum from plasma is rapid during the first four hours after intravenous administration, but then proceeds more slowly because of covalent binding to serum proteins. Levels of unbound platinum fall with a half-life of 20 minutes to 1 hour depending on the rate of drug infusion.

Elimination
The elimination of intact drug and various platinum-containing biotransformation products is via the urine. About 15-25% of administered platinum is rapidly excreted in the first 2-4 hours after administration of cisplatin. This early excretion is mostly of intact cisplatin. In the first 24 hours after administration, 20-80% is excreted, the remainder representing drug bound to tissues or plasma protein.

5.3. Pre-clinical safety data

In non-clinical repeat dose toxicity studies, renal damage, bone marrow depression, gastrointestinal disorders, ototoxicity, neurotoxicity, and immunosuppression have been observed at exposure levels similar to clinical exposure levels.

Non-clinical data indicate cisplatin is mutagenic, genotoxic and carcinogenic. Thymic lymphomas, mammary adenocarcinomas, fibro-liposarcoma, and lung adenomas were reported from repeat-dose studies of up to 19 weeks duration in mice. Leukemia and renal fibrosarcoma were reported from repeat-dose studies of up to 3 weeks in rats.

Non-clinical studies in mice showed that cisplatin caused direct damage to primordial follicle oocytes, leading to apoptosis, and ovarian depletion. Cisplatin causes testis damage and decreased sperm counts in mice, primarily through effects on differentiated spermatogonia. These findings suggest potential clinically relevant effects on male and female fertility.

Developmental toxicity studies indicate cisplatin is embryotoxic in mice and rats, and teratogenic in both species at exposure levels similar to clinical exposure levels.

Studies in rodents have shown that exposure during pregnancy can cause tumors in adult offspring.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride,
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

Do not bring in contact with aluminium. Cisplatin reacts with metal aluminium to form a black precipitate of platinum. All aluminium-containing IV sets, needles, catheters and syringes should be avoided. Cisplatin

decomposes with solution in media with low chloride content; the chloride concentration should at least be equivalent to 0.45% of sodium chloride.

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.
Antioxidants (such as sodium metabisulphite), bicarbonates (sodium bicarbonate), sulfates, fluorouracil and paclitaxel may inactivate cisplatin in infusion systems.

Cisplatin should only be used with those diluents specified in section 6.6.

6.3 Shelf life

Before opening

3 years

After dilution

Chemical and physical in-use stability after dilution with infusion fluids described in section 6.6, indicate that after dilution with recommended intravenous fluids, Cisplatin Injection remains stable for 24 hours at 20 - 25 °C room temperature. The diluted solution should be protected from light. Do not store diluted solutions in the refrigerator or freezer.

From a microbiological point of view, the diluted solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and dilution should taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Undiluted solution:
Keep container in the outer carton in order to protect from light. Do not refrigerate or freeze.

For the storage conditions of the diluted medicinal product (see section 6.3).

6.5 Nature and contents of container

For 10 ml

10 ml type I amber glass vial with a chlorobutyl grey stopper, sealed with an aluminium flip off transparent white seal/ 20 mm flip off seal transparent.

For 25 ml

30 ml type I amber glass vial with a chlorobutyl grey stopper, sealed with an aluminium flip off transparent white seal/ 20 mm flip off seal transparent.

For 50 ml
50 ml type I amber glass vial with a chlorobutyl grey stopper, sealed with an aluminium flip off transparent white seal/ 20 mm flip off seal transparent.

For 100 ml
100 mL Type I amber glass vial with a 20 mm, S127 – 4432/50 grey rubber stopper , sealed with 20 mm aluminium flip off transparent white seal/ 20 mm flip off seal transparent.

Not all pack sizes may be marketed

6.6 Special precautions for disposal

Preparation and handling of the product
Like with all anti-neoplastic products caution is needed with the processing of cisplatin. Must be diluted before use. Dilution should take place under aseptic conditions by trained personnel in an area specifically intended for this. Protective gloves should be worn for this. Precautions should be taken to avoid contact with the skin and mucous membranes. If skin contact did occur anyway, the skin should be washed with soap and water immediately. With skin contact tingling, burns and redness have been observed. In case of contact with the mucous membranes they should be copiously rinsed with water. After inhalation dyspnoea, pain in the chest, throat irritation and nausea have been reported.

Pregnant women must avoid contact with cytostatic drugs.

Bodily waste matter and vomit should be disposed with care.
If the solution is cloudy or a deposit that does not dissolve is noticed, the bottle should be discarded.

A damaged bottle must be regarded and treated with the same precautions as contaminated waste. Contaminated waste must be stored in waste containers specifically marked for this. See section “Disposal”.

Preparation of the intravenous administration
Take the quantity of the solution that is needed from the bottle and dilute with at least 1 litre of the following solutions:

- sodium chloride 0.9%
- mixture of sodium chloride 0.9% / glucose 5% (1:1), (resulting final concentrations:sodium chloride 0.45%, glucose 2.5%)
- sodium chloride 0.9% and 1.875% mannitol, for injection
- sodium chloride 0.45%, glucose 2.5% and 1.875% mannitol for injection

Always look at the injection before use. If the solution is not clear or an undissolvable precipitate is formed the solution must not be used. Only a clear solution, free from particles should be administered.

DO NOT bring in contact with injection material that contains aluminium
DO NOT administer undiluted

With respect to microbiological, chemical and physical stability with use of the undiluted solutions (see section 6.3).

Disposal
All materials that have been used for the preparation and administration, or which have been in contact with cisplatin in any way, must be disposed of according to local cytotoxic guidelines.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Limited
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United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20075/0123

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

03/01/2023